The Risk of Community-Acquired Pneumonia Among 9803 Patients with Coeliac Disease Compared to the General Population: a Cohort Study

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Abstract

Background: Coeliac Disease (CeD) patients are considered as individuals for whom pneumococcal vaccination is advocated.

Aim: To quantify the risk of community-acquired pneumonia among CeD patients, assessing whether vaccination against streptococcal pneumonia modified this risk.

Methods: We identified all CeD patients within the Clinical Practice Research Datalink linked with English Hospital Episodes Statistics between April 1997 and March 2011 and up to 10 controls per CeD patient frequency matched in 10-year age bands. Absolute rates of community-acquired pneumonia were calculated for CeD patients compared to controls stratified by vaccination status and time of diagnosis using Cox regression in terms of adjusted hazard ratios (HR).

Results: Among 9,803 CeD patients and 101,755 controls, respectively there were 179 and 1864 first community-acquired pneumonia events. Overall absolute rate of pneumonia was similar in CeD patients and controls: 3.42 and 3.12 per 1000 person-years respectively (HR 1.07, 95% CI 0.91-1.24). However, we found a 28% increased risk of pneumonia in CeD unvaccinated subjects compared to unvaccinated controls (HR 1.28, 95% CI 1.02-1.60). This increased risk was limited to those younger than 65, was highest around the time of diagnosis and was maintained for more than 5 years after diagnosis. Only 26.6% underwent vaccination after their CeD diagnosis.

Conclusions: Unvaccinated CeD patients under the age of 65 have an excess risk of community-acquired pneumonia that was not found in vaccinated CeD patients. As only a minority of CeD patients are being vaccinated there is a missed opportunity to intervene to protect CeD patients from pneumonia.

Introduction

Community-acquired pneumonia is a common and potentially serious illness, associated with considerable morbidity and mortality (1), particularly among older adult patients and those with significant comorbidities, with an overall annual incidence in the general population of the UK of 2.33 per 1000 rising to 7.99 per 1000 by age 65 years (2, 3). Streptococcus pneumonia, an encapsulated bacterium, is the most common pathogen isolated in patients with community-acquired pneumonia in Europe (4). The spleen plays an essential role in the removal of this type of bacteria in the course of initial infection, partly due to the antibodies produced by immunoglobulin M memory B cells (5). Given the high burden of pneumococcal diseases, since 1992, a 23-valent pneumococcal polysaccharide vaccination has been recommended in the UK by the Department of Health as part of the national immunisation program for individuals at risk in the general population, such as people with hyposplenism (6). One of the conditions reported as having an association with hyposplenism and therefore an impaired immunity to pneumococcus is coeliac disease (7-10). Consequently people with coeliac disease are considered as individuals for whom pneumococcal vaccination is advocated (6, 11). Given that the prevalence of clinically diagnosed coeliac disease is 0.24% in the UK and the sero-prevalence is approximately 1% (12, 13) in both children and adults this represents a potentially substantial population remaining at risk of pneumonia.

The aim of this study was to quantify the risk of community-acquired pneumonia, including pneumococcal disease, among unvaccinated and vaccinated patients diagnosed with coeliac disease compared to the general population.

Methods

Data source

The Clinical Practice Research Datalink (CPRD) (14) is a computerised primary healthcare database containing demographic, medical, prescription and lifestyle-related information of anonymised patient records from the UK. To receive health care provided free from the UK National Health Service , all residents have to be registered with a general practitioner and non-registration is estimated to be less than 0.5% (15). The data undergo various quality checks and only data of high enough quality are used for research which is denoted by the up-to-standard (UTS) date (16). Moreover, a systematic review reports a high validity of CPRD data in terms of the quality and completeness of recorded diagnoses (17). Around 53% of the CPRD practices had linked Hospital Episode Statistics (HES) data, covering the period 1997–2011 (18). HES contains details of all hospital admissions to National Health Service hospitals in England with diagnoses coded using the International Classification of Diseases version 10 (ICD-10). All records used in the study were linked to HES.

Study population

We extracted the records of subjects within the CPRD-HES linked database between 1st April 1997 and 31st March 2011, with a recorded diagnosis of coeliac disease. Coeliac disease was defined based on the presence of one or more of the following Read codes (a clinically coded thesaurus used by general practitioners in the UK to record medical information that includes diagnostic codes based on ICD-10 and additional information): J690.00 Coeliac Disease; J690.13 Gluten enteropathy; J690z00 Coeliac disease NOS; J690100 Acquired coeliac disease; J690.14 Sprue-nontropical; J690000 Congenital coeliac disease, using previously defined methodology (13). Patients could have a diagnosis of both coeliac disease and dermatitis herpetiformis, but not dermatitis herpetiformis alone. For patients with more than one coeliac disease code, the earliest was considered as the date of disease diagnosis. All

remaining people without diagnosis of coeliac disease in the same CPRD-HES population were potential controls. From these, we excluded controls with any record of gluten free prescription in the absence of a coeliac disease diagnosis, or those with only dermatitis herpetiformis codes. A random follow-up start date "pseudo-diagnosis-date" was generated between the date of birth and study end date for each control (as defined in our previous study(19)). This random pseudo-diagnosis-date enabled us to calculate an index age for controls which was used to frequency match age at diagnosis of patients with coeliac disease in 10-year age bands at the ratio of ten controls to one patient.

Follow-up time

We used an open cohort approach where individuals could enter and exit the study at different points in time. The study start date was defined as the latest of 1st April 1997 (date of HES linkage), UTS date, patient's current registration date and coeliac disease diagnosis date (or pseudo-diagnosis-date for controls) whereas the study end date was considered as the earliest of 31st March 2011, patient's transfer out date from the practice, last date of data collection from practice, date of death and first community-acquired pneumonia event.

Community acquired infective pneumonia

Patients were defined as having incident pneumonia if they had an ICD-10 code, and/or a Read code suggesting pneumonia (Supplementary Table 1). Pneumonia diagnoses recorded less than 28 days apart were regarded as the same event. This cut-off period was based on the previous literature (3) and the initial examination of our data. For the events with more codes recorded within 28 days, the earliest pneumonia date and the last pneumonia aetiology's code were used. We also excluded pneumonia cases diagnosed within 30 days of a patient's registration with their practice as these might represent historical records being coded at first

visit post registration (20). We only considered the first occurrence of pneumonia during the study period excluding all subsequent pneumonia events and all subjects with a previous history of pneumonia. To restrict our cases to only those with community-acquired pneumonia, we excluded all potential hospital-acquired infections by keeping only hospital admissions where the first primary diagnosis (reason for admission) was for pneumonia and excluding all pneumonia records within 14 days after hospital discharge in either primary or secondary care, consistently with what has been described in previous studies (3, 21, 22) (Supplementary Figure 1**)**. Finally, we separately analysed the first incidence of community-acquired pneumonia specifically restricted to pneumococcal infection (pneumococcal code: Lobar (pneumococcal) pneumonia (Read code=H21..00), Lobar pneumonia, unspecified (ICD-10=J181, Read code=H260.00), Pneumonia due to Streptococcus pneumoniae (ICD-10=J13) and Chest infection- pneumococcal pneumonia (Read code=H21..11)).

Pneumococcal vaccination

We extracted information on patients' pneumococcal vaccination status during the study period from their medical records (Read codes or prescription indicating pneumococcal vaccination; Supplementary Table 2). For patients with more than one vaccination code, the earliest was considered as the date of vaccination. The follow-up time for each patient was divided as either "vaccinated" (time after the date of vaccination) or "unvaccinated" (time period preceding the date of vaccination). The latter time period also included all follow-up time of those with no record of pneumococcal vaccination (Figure 1).

Covariates

Covariates included sex, age (0-64 and ≥ 65), calendar-year (1997-2004 and 2005-2011), body mass index (BMI Kg/m^2), smoking status (non-smokers, including ex-smokers and missing data, and current smokers), socioeconomic status, number of comorbidities on the

basis that all could be potentially related to coeliac disease and pneumonia(2, 3, 23-26) . We extracted all covariates data from CPRD. BMI was classified as underweight (≤ 18.5), normal weight (>18.5-25), overweight (>25-30) and obese (>30). Comorbidities were defined using the Charlson index (27), details of which are reported elsewhere (28), and categorised as no comorbidity (Charlson index=0) or more than one comorbidity (Charlson index≥1). We considered the last record reported in CPRD before the study end for smoking, BMI and comorbidities. Socioeconomic status was categorised by the quintile of the rank of a patient's area of residence by the Indices of Multiple Deprivation (29).

Statistical analysis

We calculated overall pneumonia rates per 1000 person-years among subjects with and without coeliac disease. We assessed unvaccinated and vaccinated periods of time separately. We then used a Cox regression model to estimate the hazard ratios (HR) of community-acquired pneumonia during unvaccinated and vaccinated periods in patients with coeliac disease after diagnosis compared to controls after testing for the proportional hazards assumption. All HRs were adjusted for sex, age, calendar-year, BMI, smoking status, socioeconomic status, and number of comorbidities (when the models were not stratified by these variables). We assessed for possible interactions between coeliac disease and all of the above covariates using a likelihood ratio test (LRT).

We then assessed how rates of pneumonia in unvaccinated patients varied in relation to the time of coeliac disease diagnosis (Figure 1). For this analysis we used person-time for the overall study period, removing the coeliac disease diagnosis date (or pseudo-diagnosis-date for controls) from our main start date definition. We excluded patients diagnosed with coeliac disease within 1 year of their registration with the practice, as these may represent the recording of historical diagnoses during the first visits post registration (20). We assessed

the risk of pneumonia in the time periods before diagnosis of coeliac disease (within 1 year before and more than 1 year before), within 1 year after diagnosis, between 1 and 4 years after and more than 5 years after. The last two periods also included person time of those with a historical record of coeliac disease (Supplementary Figure 2). For each period we calculated the absolute excess risk of pneumonia among unvaccinated patients with coeliac disease compared to unvaccinated controls. Finally, we restricted analysis to the outcome of pneumococcal pneumonia specifically using similar methodology. All analyses were performed using Stata version12, Stata Corp., College Station, TX.

Sensitivity analysis

We increased the specificity of our coeliac disease definition by repeating our analysis for community-acquired pneumonia after restricting our population with coeliac disease to those who, in addition to one diagnostic code of coeliac disease, had either a relevant prescription for a gluten-free product or a second documented record of their disease.

Results

Our cohort was composed of 9,803 patients with coeliac disease and 101,755 controls, who contributed 52,362 and 595,866 person-years at risk, respectively (Table 1). The median follow-up from the study start to end date was 4.2 years (Interquartile range (IQR) 1.7-9.1) in patients with coeliac disease and 4.6 years (IQR 1.8-9.8) in controls. There were 179 and 1864 first community-acquired pneumonia events recorded in patients with coeliac disease and controls, respectively. The overall rate of community-acquired pneumonia events was 3.42 per 1000 person-years in patients with coeliac disease and 3.12 per 1000 person-years among controls. Overall patients with coeliac disease had no increased risk of community-acquired pneumonia events compared to controls (adjusted HR 1.07, 95% CI 0.91-1.24).

Community-acquired pneumonia risk in unvaccinated and vaccinated periods

Thirty-seven percent of patients with coeliac disease and 22.6% of controls underwent pneumococcal vaccination. The average age at the time of vaccination was 61.8 years (IQR 45.6-69.57) in patients with coeliac disease and 67.5 (IQR 60.7-74.4) in controls. Patients with coeliac disease and controls subjects who underwent vaccination were older and had more comorbidities compared to unvaccinated subjects (Table 1). Among patients with coeliac disease 26.6% underwent vaccination after their coeliac disease diagnosis with 3.02% being vaccinated within 1 year following diagnosis and before 65 years of age. The average time from coeliac disease diagnosis to the pneumococcus vaccination was 6.7 years (IQR 2.2-16.2). The median time from vaccination to pneumonia event was 4.33 years (IQR 2.22-7.11).

In unvaccinated patients we observed an absolute risk of pneumonia of 2.36 per 1000 person-years in patients with coeliac disease compared to 2.01 per 1000 person years in controls, corresponding to an increased relative risk of pneumonia of 28% (HR 1.28, 95% CI 1.02-1.60) (Table 2 and Table 3). This difference persisted in the following subgroups: males (HR 1.55, 95% CI 1.02-2.18), subjects younger than 65 years (HR 1.68, 95% CI 1.28-2.21), subjects with normal BMI (HR 1.75, 95% CI 1.29-2.39), in the period between 1997 and 2004 (HR 1.52, 95% CI 1.13-2.05) and in subjects from the least deprived areas (HR 1.55, 95% CI 1.01-2.38), (Table 3). In vaccinated subjects we observed an absolute risk of pneumonia of 6.04 and 8.65 per 1000 person-years in subjects with coeliac disease and controls respectively. In this subgroup we observed no overall difference in risk of pneumonia (HR 0.88, 95% CI 0.70-1.10) in patients with coeliac disease compared to controls, except for vaccinated patients with coeliac disease younger than 65 years who had 53% lower risk than vaccinated controls of the same age (HR 0.47, 95% CI 0.27-0.84). Finally, there was a significant interaction between coeliac disease and age categorised as 0-64 and $\geq$ 65 in unvaccinated subjects (LRT p value <0.001), while there were no other significant interactions between coeliac disease and the other covariates. All HRs were adjusted for sex, age (0-64, $\geq$65), calendar-year, BMI, smoking status, Charlson index and SES (when not stratified for). Even using the age variable categorised in three rather than two bands for adjustment (0-17, 18-64 and $\geq$65) the risk of pneumonia in patients with coeliac disease compared to controls did not change materially.

Figure 2 shows the cumulative incidence of pneumonia in patients with coeliac disease and controls in overall period (Figure 2a) and in unvaccinated period (Figure 2b).

Risk of first community-acquired pneumonia and pneumococcal pneumonia before and after coeliac disease diagnosis in unvaccinated subjects

Having detected a statistically significant higher risk of pneumonia in unvaccinated patients with coeliac disease compared to unvaccinated controls and a significant interaction with age, we limited the analysis to time when patients were unvaccinated and aged less than 65 years (Table 4) and we adjusted our analysis for sex, age (3 age-bands: 0-17, 18-49, 50-64), calendar year, BMI, smoking status, Charlson index and SES. We observed a 5.09 fold higher risk of community-acquired pneumonia within the year before coeliac disease diagnosis (HR 5.09, 95% CI 2.92- 8.18) and a 2.51 fold higher risk in the year after (HR 2.51, CI 1.11-5.62) compared to the general population. These corresponded to an absolute excess risk of pneumonia of 3.63 and 1.26, respectively. The elevated risk was maintained for more than 1 year before and well over 5 years after diagnosis (Table 4). We found similar results when considered pneumococcal pneumonia specifically. In particular we detected a 5.32 fold higher risk of streptococcal pneumonia within the year before coeliac disease diagnosis (HR 5.32, 95% CI 2.17- 13.04) and a 4.58 fold higher risk in the year after (HR 4.58, CI 1.69-12.44) compared to the general population.

Sensitivity analysis

Seventy-six percent of patients with coeliac disease received a relevant prescription for a gluten-free product and/or a second documented record of their disease. Restricting our population to these patients, we found similar findings for all community-acquired pneumonia and pneumococcal pneumonia specifically (**Supplementary Table 3**).

Discussion

In this large, population-based cohort study of people with coeliac disease in England, 37% had evidence of having ever received pneumococcal vaccination and only 26% following diagnosis. Among unvaccinated individuals under the age of 65, those with coeliac disease had an increased risk of community-acquired pneumonia compared to unvaccinated individuals without coeliac disease. However, among vaccinated individuals of this age, patients with coeliac disease were less likely to have pneumonia compared to vaccinated individuals without coeliac disease. The increase in risk among the unvaccinated was highest in the period around coeliac disease diagnosis, being approximately 2-fold higher for any infective pneumonia and 4-fold higher for pneumococcal pneumonia but the risks also persisted up to at least 5 years following diagnosis.

Strengths and Limitations

Ours is the largest study of pneumonia risk in patients with coeliac disease published to date and has allowed us therefore to precisely quantify both relative and absolute risks while adjusting for important potential confounders during periods of time around and beyond diagnosis. Our use of contemporary, nationally representative primary care data linked to secondary care data, collected prospectively during routine clinical care, makes our findings generalisable to most current patients with clinically diagnosed coeliac disease. In addition, these linked data have allowed us to substantially improve upon the current evidence in this area as we had the ability to define both vaccination status and pneumonia that did not necessarily require hospital admission. These two issues have not previously been accounted for due to the reliance on hospital admission data alone in the previous research (25, 26).

Several potential weaknesses regarding our study design must be considered. As with almost all research that utilises electronic health record data we are reliant on the accuracy and validity of the recording of the exposures, outcomes and covariates we have used. For coeliac disease the recording in primary care has previously been specifically validated (30). Several studies have used this definition and found similar findings with respect to outcomes such as incidence, fracture risk and death (13, 31, 32) implying it is adequate for research purposes. Nevertheless to check the robustness of our findings with respect to the specificity of the definition of coeliac disease we repeated our analyses using a more restricted definition that relied upon further evidence of coeliac disease being present in the primary care record. When we did this our results remained largely unaltered. Our definition of community-acquired pneumonia was based on a recently published study that used CPRD-HES linked data to describe the incidence of the disease among people over the age of 65 (3, 33).Unsurprisingly therefore we found a similar incidence rate of community-acquired pneumonia among our controls aged more than 65 years. Our general population rates are also consistent with another UK paper that has described the incidence of pneumonia in the general population (2). Furthermore, a previous validation study showed that the use of routine primary health-care databases in the UK are a valid way for identification of pneumonia (34). Our results are based on analysis of a relatively small number of events, which may influence the overall results and account for the large confidence intervals, however as reported above, they are consistent with those reported in the previous literature (2, 3). We observed a higher risk of pneumonia in vaccinated people compared to unvaccinated subjects. This higher risk might be due to the fact that vaccinated subjects were older and had more comorbidities than those unvaccinated and thus they may have a higher risk of any type of pneumonia. Although a recent review has shown that Streptococcus pneumoniae is the more frequent cause (4), another explanation

for the higher risk of pneumonia in vaccinated subjects may be that community-acquired pneumonia may be related to other microorganisms unaffected by vaccination. In terms of vaccination status we believe that it is highly unlikely that general practitioners would not record the vaccination at the time of its prescription or incorrectly record the fact of vaccination when, in truth, it did not occur. It is possible though that prior to registering at a CPRD practice some people in our study could have received a vaccination but this information was not transferred electronically on registering with their new general practitioner. If present this bias would result in an underestimation of the proportion of people vaccinated but it seems unlikely to us that such recording would have been differential between people with coeliac disease and controls and any effect of this would be to introduce a null bias in the relative risk of pneumonia between these groups. Finally, the slightly higher risk of community acquired pneumonia reported in the unvaccinated sub-groups with coeliac disease normally considered at "low risk" (normal BMI, last deprived SES and younger age group) compared to unvaccinated controls is probably due to the fact that coeliac disease is the only recognised and recorded factor indicating their status of higher risk subjects. Moreover, it may be related to the low event rate in the relevant control group because they are essentially healthy. Of note, we found a higher absolute risk of pneumonia in males than females, that has been already described in the previous literature (3). Our study is limited to clinically diagnosed people with coeliac disease and it lacked information regarding the severity of coeliac disease at diagnosis and any estimate of splenic function. Inevitably therefore we could not assess the risks of pneumonia among subgroups of people who might be more at risk due to more severe illness or relatively poor splenic function.

Previous literature

Whilst two previous studies have quantified the risk of pneumococcal infection in coeliac disease compared to the general population, none have assessed community-acquired pneumonia risk and none have been able to assess vaccination status. A Swedish population-based study (26), of 15,000 individuals (mostly children) with an inpatient diagnosis of coeliac disease from 1964-2003 compared with controls showed that coeliac disease was associated with an increased risk of pneumococcal sepsis (HR 3.9, 95% CI 2.2-7.0) which is not dissimilar to our estimate for pneumococcal pneumonia in the unvaccinated population around diagnosis. However, in this study, the authors were only able to use hospital data to assess severe cases of pneumococcal sepsis. No information on vaccination status was available. Thomas et al. analysed the risk of invasive pneumococcal infection in coeliac disease compared to the general population of England (25). The authors used the Oxford Record Linkage Study covering the period from 1963 to 1999 (preceding the era of pneumococcal vaccination) to identify people with coeliac disease and had linked HES and Office for National Statistics death data, spanning April 1st 1998 to March 31st 2003 for the purposes of follow up. The risk for pneumococcal infections in patients with coeliac disease compared to the general population was approximately 2-fold higher and this increased risk was described both within a year of coeliac disease diagnosis and after more than one year. However, they also had no information on which individuals had had vaccination.

Interpretation

There are several possible explanations for the excess risk of community-acquired pneumonia among people with coeliac disease that we have observed. The first is ascertainment bias as people with coeliac disease have reason to have more health care

attendances than the general population both prior to diagnosis and afterwards . These extra visits give opportunities for health care practitioners to assess, diagnose, treat and record conditions that otherwise may have gone unnoticed and might explain the increased risk we found around the time of diagnosis. However, community-acquired pneumonia is a reasonably severe disease that would presumably result in patients seeking treatment from their doctors, and the increased risk of pneumonia prior to diagnosis might actually reflect an increased risk of pneumonia consequent to covert disease manifestation in patients with untreated coeliac disease. During the period around the diagnosis of coeliac disease some people have impaired nutritional status which may increase the risk of respiratory infections (35-37). Conversely, when a person gets diagnosed with community-acquired pneumonia it is common for them to undergo a series of blood tests which may identify abnormalities that could eventually lead to a diagnosis of coeliac disease. However our analysis shows that the increased risk of pneumonia persists even 5 years after diagnosis.

Beyond ascertainment bias there are biologically plausible explanations for the increase in risk, one of which is the previously reported association between coeliac disease and hyposplenism. Several studies have attempted to quantify the occurrence and severity of this but most of them are prior to 1990, most suffer from selection bias in terms of their patient population (they are tertiary referral centres) and have used approaches to splenic function measurement that have high error/inaccuracy (7-10, 38-40). Nevertheless, the best evidence from these studies indicates that almost one third of adult patients with coeliac disease have some biological/clinical evidence splenic dysfunction which seems to improve on a gluten free diet (8, 9), it does not affect childhood coeliac disease (7) and it is more frequent in people with coeliac disease with associated autoimmune diseases and

with other complications (refractory coeliac disease, lymphoma, ulcerative jejunoileitis) (10).

Implications for clinical practice

We have found that unvaccinated people under the age of 65 with coeliac disease have an excess risk of community-acquired pneumonia and specifically pneumococcal pneumonia. Our work shows that only 26.6% underwent vaccination after an average time of 6.7 years from coeliac disease diagnosis. In the patient group with the highest relative risk, those under age 65 years, only 3.02% were vaccinated within the year following their coeliac disease diagnosis. The interpretation of this finding must take into account the fact that our study spans a long period of time in which diagnostic practises have changed with respect to coeliac disease and there may be some inaccuracy in the time between vaccination and diagnosis in the "prevalent" population. Nevertheless, although the percentage of vaccinated patients with coeliac disease is higher compared to that reported by Pebody et al (41), our study reveals a potential missed opportunity to help prevent community-acquired pneumonia and, in particular, pneumococcal pneumonia among the majority of people with coeliac disease. This is despite recommendations from the Department of Health/Public Health England advising pneumococcal vaccination for those under the age of 65 who are potentially at risk due to splenic hypofunction (6) and complementary disease specific guidelines for coeliac disease advocating a similar approach (11).

Conclusion

Our study represents further evidence of an ongoing low rate of pneumococcal vaccinations in people with coeliac disease despite a higher risk of pneumonia compared to the general population. Given the safety and efficacy of the vaccination and the difficulty in "risk stratifying" among people with coeliac disease, we believe that the recommended vaccinate all strategy seems sensible.

Fig. 1. Study periods: Follow-up time of patients with coeliac disease and vaccination status

Fig 2: Cumulative incidence of pneumonia in patients with coeliac disease and controls in overall period (Figure 2a) and in unvaccinated period (Figure 2b)

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1 **Table 1: Demographic Details of the Study Population (N 111,558)**

	Overall population		Unvaccinated population		Vaccinated population	
	With CeD (n=9,803)	**Controls (n=101,755)**	**With CeD (n=6,160)**	**Controls (n=78,697)**	**With CeD (n=3,643)**	**Controls (n=23,058)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Female	6,383 (65.1)	52,141 (51.2)	4,017 (65.1)	39,935 (50.7)	2,366 (64.9)	12,206 (52.9)
Age at CeD Diagnosis/ Pseudo-date (yr)						
0-64	8,018 (81.8)	83,129 (81.7)	5,757 (93.5)	71,286 (91.6)	2,261 (62.1)	11,843 (51.4)
≥65	1,785 (18.2)	18,626 (18.3)	403 (6.5)	7,411 (9.4)	1,382 (37.9)	11,215 (48.6)
BMI						
≤ 18.5	477 (4.9)	2,098 (2.1)	286 (4.6)	1,534 (1.9)	191 (5.2)	564 (2.4)
>18.5-25	4,528 (46.2)	33,905 (33.3)	2,769 (44.9)	26,518 (33.7)	1,759 (48.3)	7.387 (32.1)
>25-30	1,778 (18.1)	20,662 (20.3)	1,017 (16.6)	14,718 (18.7)	761 (20.9)	5,944 (25.8)
>30	1,183 (12.1)	17,904 (17.6)	658 (10.7)	12,255 (15.6)	525 (14.4)	5,649 (24.5)
Unknown	1,837 (18.7)	27,186 (26.7)	1,430 (23.2)	23,672 (30.1)	407 (11.2)	3,514 (15.2)
Smoking						
Non-smokers	8,430 (86.0)	82,725 (81.4)	5,137 (83.5)	62,164 (79.0)	3,293 (90.4)	20,561 (89.2)
Current smokers	1,373 (14.0)	19,030 (18.6)	1,023 (16.5)	16,533 (21.0)	350 (9.6)	2,497 (10.8)
SES						
Least deprived	2,647 (27.0)	22,931 (22.5)	1,647 (26.7)	17,826 (22.7)	1000 (27.4)	5,105 (22.1)
2	2,343 (23.9)	22,763 (22.4)	1,480 (24.1)	17,322 (22.0)	863 (23.8)	5,441 (23.6)
3	1,873 (19.1)	19,162 (18.8)	1,147 (18.6)	14,722 (18.7)	726 (19.9)	4,440 (19.3)
4	1,625 (16.5)	19,427 (19.1)	1,031 (16.7)	15,302 (19.4)	594 (16.3)	4,125 (17.9)
Most deprived	1,097 (11.3)	14,144 (13.9)	725 (11.8)	11,211 (14.3)	372 (10.2)	2,933 (12.7)
Unknown	218 (2.2)	3,328 (3.3)	130 (2.1)	2,314 (2.9)	88 (2.4)	1,014 (4.40)
Charlson index						
0	5,629 (57.4)	67,599 (66.4)	4,165 (67.6)	59,645 (75.8)	1,464 (40.2)	7,954 (34.5)
≥1	4,174 (42.6)	34,156 (33.6)	1,995 (32.4)	19,052 (24.2)	2,179 (59.8)	15,104 (65.5)

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Table 2: Rate of first community-acquired pneumonia during unvaccinated and vaccinated periods of time in patients with coeliac disease after diagnosis and in controls

	First community-acquired Pneumonia							
	Overall		Unvaccinated period			Vaccinated Period		
	Rates in CeD[a]	Rates in Controls[a]	N events in CeD/ Controls	Rates in CeD[a]	Rate in Controls[a]	N events in CeD/ Controls	Rates in CeD[a]	Rates in Controls[a]
Overall	3.42	3.12	**88/996**	2.36	2.01	**91/868**	6.04	8.65
Sex								
Male	4.23	3.08	**37/455**	2.85	1.85	**40/446**	7.62	9.63
Female	2.98	3.16	**51/541**	2.09	2.16	**51/422**	5.19	7.81
Age (years)								
0-64	1.94	1.17	**63/410**	1.91	1.00	**15/96**	2.09	4.58
≥65	8.25	8.20	**25/586**	5.78	6.80	**76/772**	9.61	9.72
Calendar-year								
1997-2004	3.20	2.73	**48/562**	2.80	2.18	**16/205**	5.59	8.81
2005-2011	3.55	3.47	**40/434**	1.98	1.82	**75/663**	6.14	8.60
BMI								
≤ 18.5	6.61	8.09	**6/41**	3.46	4.49	**11/54**	13.14	20.65
>18.5-25	3.95	3.02	**48/301**	2.85	1.76	**48/320**	6.45	9.25
>25-30	1.91	2.65	**9/182**	1.27	1.63	**11/189**	3.28	6.64
>30	2.48	2.52	**7/142**	1.50	1.43	**10/175**	4.57	6.57
Unknown	3.51	4.04	**18/330**	2.57	3.12	**11/130**	5.73	16.16
Smoking								
Non-smoker	3.29	3.02	**69/765**	2.16	1.89	**81/730**	5.91	8.08
Smoker	4.26	3.64	**19/231**	3.49	2.53	**10/138**	7.29	13.79
SES								
Least deprived	3.17	2.36	**25/189**	2.36	1.56	**22/150**	5.19	6.63
2	3.51	2.94	**22/213**	2.38	1.82	**23/202**	6.40	8.41
3	2.98	3.06	**13/197**	1.82	2.07	**17/153**	5.76	7.95
4	3.44	3.48	**16/199**	2.68	2.21	**13/177**	5.29	9.69
Most deprived	4.72	3.86	**10/149**	2.54	2.39	**16/140**	10.22	11.20
Unknown	2.68	6.65	**<5/49**	4.25	4.65	**<5/46**	-	12.26
Charlson Index								
0	1.16	1.12	**26/321**	1.10	0.95	**8/88**	1.40	3.12
≥1	6.25	6.25	**62/675**	4.48	4.20	**83/780**	8.87	10.80

a per 1000 person-years

Table 3: Risk of first community-acquired pneumonia during unvaccinated and vaccinated periods of time in patients with coeliac disease after diagnosis compared to controls

First community-acquired Pneumonia				
	Unvaccinated period		Vaccinated period	
	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Overall	1.16 (0.93 to 1.45)	1.28 (1.02 to 1.60)	0.71 (0.57 to 0.88)	0.88 (0.70 to 1.10)
Sex				
Male	1.52 (1.08 to 2.12)	1.55 (1.10 to 2.18)	0.79 (0.57 to 1.10)	0.94 (0.68 to 1.31)
Female	0.96 (0.72 to 1.29)	1.13 (0.85 to 1.52)	0.68 (0.51 to 0.91)	0.83 (0.61 to 1.12)
Age groups				
0-64	1.90 (1.45 to 2.47)	1.68 (1.28 to 2.21)	0.45 (0.26 to 0.78)	0.47 (0.27 to 0.84)
≥65	0.83 (0.56 to 1.24)	0.83 (0.55 to 1.24)	0.97 (0.77 to 1.23)	0.98 (0.77 to 1.25)
Calendar-year				
1997-2004	1.27 (0.94 to 1.71)	1.52 (1.13 to 2.05)	0.64 (0.38 to 1.06)	0.89 (0.53 to 1.50)
2005-2011	1.09 (0.79 to 1.51)	1.05 (0.76 to 1.46)	0.73 (0.57 to 0.93)	0.86 (0.67 to 1.10)
BMI				
≤ 18.5	0.77 (0.32 to 1.82)	0.91 (0.37 to 2.18)	0.74 (0.38 to 1.43)	0.77 (0.39 to 1.52)
>18.5-25	1.61 (1.19 to 2.18)	1.75 (1.29 to 2.39)	0.71 (0.52 to 0.96)	0.96 (0.70 to 1.32)
>25-30	0.78 (0.40 to 1.54)	0.96 (0.49 to 1.89)	0.51 (0.27 to 0.93)	0.75 (0.41 to 1.40)
>30	1.07 (0.50 to 2.30)	1.19 (0.55 to 2.57)	0.73 (0.38 to 1.39)	0.97 (0.51 to 1.86)
Unknown	0.82 (0.51 to 1.32)	1.04 (0.65 to 1.68)	0.52 (0.28 to 0.97)	0.76 (0.40 to 1.41)
Smoking				
Non-smokers	1.13 (0.88 to 1.45)	1.27 (0.99 to 1.64)	0.75 (0.59 to 0.94)	0.88 (0.69 to 1.11)
Current smokers	1.38 (0.86 to 2.20)	1.34 (0.83 to 2.15)	0.53 (0.28 to 1.00)	0.94 (0.48 to 1.84)
SES				
Least deprived	1.50 (0.98 to 2.28)	1.55 (1.01 to 2.38)	0.80 (0.50 to 1.25)	1.02 (0.64 to 1.63)
2	1.29 (0.83 to 2.00)	1.33 (0.85 to 2.08)	0.77 (0.49 to 1.19)	0.95 (0.61 to 1.48)
3	0.87 (0.49 to 1.53)	1.03 (0.59 to 1.83)	0.73 (0.44 to 1.21)	0.92 (0.55 to 1.54)
4	1.20 (0.72 to 2.00)	1.33 (0.79 to 2.22)	0.56 (0.31 to 0.98)	0.64 (0.36 to 1.15)
Most deprived	1.07 (0.56 to 2.02)	1.16 (0.61 to 2.24)	0.92 (0.54 to 1.55)	1.00 (0.59 to 1.72)
Unknown	0.90 (0.22 to 3.74)	0.86 (0.20 to 3.58)	-	-
Charlson index				
0	1.14 (0.77 to 1.71)	1.24 (0.82 to 1.85)	0.42 (0.20 to 0.87)	0.58 (0.27 to 1.25)
≥1	1.06 (0.81 to 1.37)	1.28 (0.99 to 1.67)	0.85 (0.67 to 1.06)	0.93 (0.73 to 1.17)

a: adjusted for sex, age, calendar-year; BMI; smoking; Charlson index, SES (when not stratified for);
Reference is controls' group
HR, Hazard ratio; CI, confident interval

Table 4: Risk of community-acquired and pneumococcal pneumonia in unvaccinated patients with coeliac disease (in relation to the time of diagnosis) compared to unvaccinated controls (subjects younger than 65 years old)

	First community-acquired pneumonia Total population= 81,166					Pneumococcal Pneumonia Total population=82,088				
Time period	**N events in CeD**	**Rate in CeD[a]**	**Absolute Excess risk**	**Unadjusted HR**	**Adjusted HR[b]**	**N events in CeD**	**Rate in CeD[a]**	**Excess risk**	**Unadjusted HR**	**Adjusted HR[b]**
Before diagnosis										
+1 year	**21**	1.43	0.44	1.45 (0.93 to 2.24)	1.73 (1.11 to 2.70)	**8**	0.53	0.2	1.55 (0.76 to 3.16)	1.75 (0.85 to 3.60)
within 1 year	**13**	4.62	3.63	4.66 (2.68 to 8.10)	5.09 (2.92 to 8.18)	**5**	1.74	1.41	5.24 (2.15 to 12.79)	5.32 (2.17 to 13.04)
After diagnosis										
within 1 year	**6**	2.28	1.29	2.33 (1.04 to 5.21)	2.51 (1.11 to 5.62)	**<5**	1.49	1.16	4.58 (1.69 to 12.39)	4.58 (1.69 to 12.44)
1-4 years	**19**	2.12	1.13	2.14 (1.35 to 3.39)	2.11 (1.33 to 3.35)	**7**	0.76	0.43	2.30 (1.07 to 4.91)	2.30 (1.07 to 4.95)
+ 5 years	**31**	1.59	0.6	1.60 (1.11 to 2.31)	1.67 (1.15 to 2.41)	**8**	0.40	0.07	1.22 (0.60 to 2.49)	1.21 (0.59 to 2.49)

a: per 1000 person-years;
b: adjusted for sex, age (3 age-bands : 0-17, 18-49, 50-64), calendar year; BMI; smoking; Charlson index SES; Reference is controls group
reference group: 445 events, overall incidence rate 0.99 per 1000 person-years (community-acquired infective pneumonia)
reference group: 153 events, overall incidence rate 0.33 per 1000 person-years (pneumococcus pneumonia)

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